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Colchicine as adjuvant therapy in COVID-19 patients: a meta-analysis

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ABSTRACT

SARS-CoV-2 infection results in hyperinflammatory responses by activating proinflammatory cytokines and chemokines. Colchicine is an anti-inflammatory drug that reduces superoxide production, tumor necrosis factor alpha (TNF-α) activation, and neutrophil chemotaxis. This study aimed to understand the effect of adjuvant colchicine on mortality in COVID-19 patients. Systematic literature searching was conducted on PubMed, ScienceDirect, Cochrane Library, and medRxiv with keywords colchicine, coronavirus disease, COVID-19, mortality, and SARS-CoV-2. Five randomized controlled studies with 15,779 patients were included. There was no significant difference between the colchicine group and the standard group (OR 1.00 [95% CI 0.91-1.09], p=0.94); invasive mechanical ventilation necessity also did not show a significant difference (OR 0.99 [95% CI 0.83-1.17 p=0.88). There was no significant difference in the incidence of cardiovascular disease (OR 1.11 [95% CI 0.50-2.46], p=0.79), also the incidence of pneumonia was lower in colchicine group (OR 0.68 [95% CI 0.49-0.93], p=0.02), while the incidence of gastrointestinal complaints was higher in colchicine group (OR 2.09 [95% CI 1.84-2.37], p<0.00001). Colchicine as COVID-19 adjuvant therapy did not significantly reduce mortality, the need for invasive mechanical ventilation, and the incidence of cardiovascular disease. Furthermore, the colchicine group had lower pneumonia incidence and higher gastrointestinal complaint incidence.

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1. INTRODUCTION

Studies related to coronavirus disease 2019 (COVID-19) are still evolving. COVID-19 case fatality rate is approximately 1-3% [1]. Severe COVID-19 mostly manifested as acute respiratory distress syndrome (ARDS) and it has been linked to cytokine storms by upregulation of chemokines and other cytokines [2]–[5]. The main cytokines involved are interleukins (ILs), interferons (IFNs), tumor necrosis factors (TNFs), and colony-stimulating factors (CSFs) [6]. IFN-γ and Tumor Necrosis Factor Alpha (TNF-α) cause lung damage, vascular leakage, heart failure, and acute protein phase synthesis. IL-6 causes vascular leak syndrome, coagulation, obstruction of small blood vessels, and cardiomyopathy [7], [8]. It is essential to

conduct further studies about anti-inflammatories as an additional SARS-CoV-2 infection treatment, due to the positive effects of immunosuppressive agents, especially in critically ill patients [9], [10].

Colchicine is an anti-inflammatory drug that inhibits neutrophil chemotaxis, adhesion, superoxide production, and TNF activation. It causes downregulation of various pathways of inflammatory and modulates innate immunity. The other mechanisms include the inhibitory effect of macrophages and stimulation of dendritic cell maturation [11], [12]. The study of this agent is promising because it acts on multiple targets related to hyperinflammation in COVID-19 [12]. We intended to determine the relationship between colchicine and COVID-19 mortality.

2. RESEARCH METHOD

This study conducted according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines as shown in Figure 1 [13]. A literature search was performed on PubMed, ScienceDirect, Cochrane, and medRxiv. The keywords included were colchicine, coronavirus disease, COVID-19, SARS-CoV-2, and mortality.

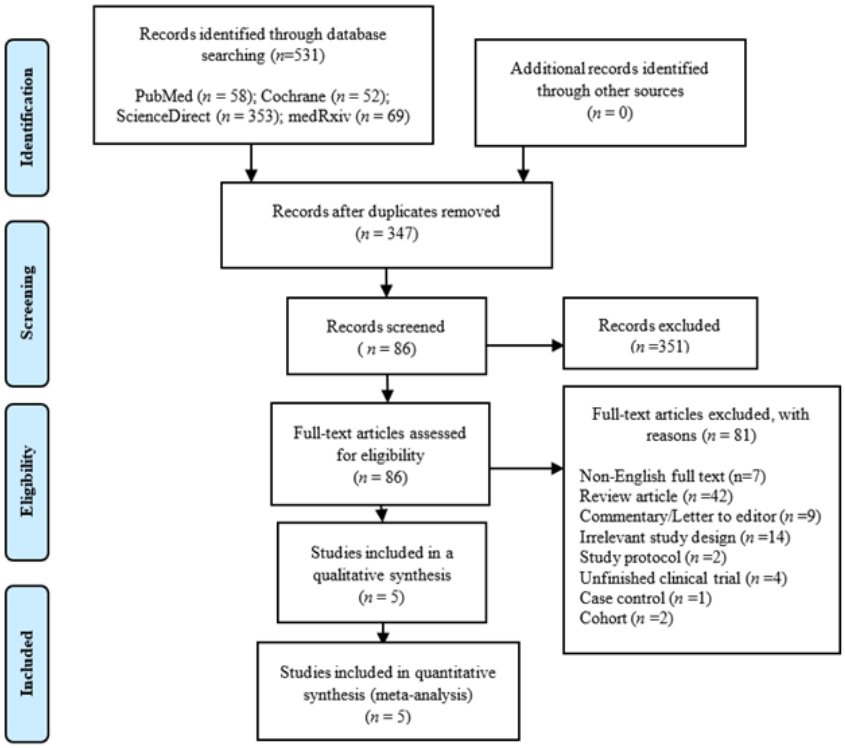

Figure 1. Study selection flow diagram (PRISMA)

The following studies met the inclusion criteria: i) Study design: Randomized clinical trial; ii) Laboratory-confirmed SARS-CoV-2 patients or clinically suspected COVID-19 (hospitalized or non-hospitalized); iii) Colchicine administration; iv) Placebo, standard of care (SOC), without colchicine; v) Primary outcome: mortality; and vi) Secondary outcome: any outcome variable. Exclusion criteria included: i) Incomplete data, ii) No reporting of outcome variables, and iii) Pediatric or pregnant woman population. The articles were collected in a citation manager. After excluding duplicate articles, we screened titles and abstracts, then investigated selected full-text articles. The results analyzed were: mortality rate, invasive mechanical ventilation necessity, cardiovascular events, gastrointestinal symptoms as colchicine side effects, and pneumonia events. The quality of studies was evaluated using Cochrane collaboration tools for assessing risk of bias [14].

Review Manager (RevMan) version 5.4 was performed for analysis. For dichotomous variables, the odds ratio (OR) was used to determine effect size, while continuous variables were calculated as mean differences (MD). The odds ratio (OR) was calculated using a random-effects model with a 95% confidence interval (CI). Heterogeneity between each study was assessed using the I-squared (I^2) test, I^2>50% was indicative of substantial heterogeneity. Furthermore, $p<0.05$ was considered significant.

3. RESULTS AND DISCUSSION

3.1. Baseline characteristic feature

Five articles with 15,779 eligible patients were obtained from databases [15]–[19], consisting of 7,828 patients treated with colchicine and 7,951 patients treated with SOC without colchicine. The characteristics and results studies were shown in Table 1. Cochrane collaboration tools for assessing bias risk were used to assess the quality of included randomized controlled trials (RCTs). All of the included RCTs showed a low risk of bias as shown in Figure 2.

Table 1. Characteristics of included studies

References	Case (colchicine vs comparator	Study design	Study population	Colchicine Dose	Comparator	Outcome evaluated
[16]	55 vs 50	RCT open-label	Hospitalized patients	1.5 mg followed by 2 x 0.5 mg per day until discharge or 21 days	SOC	Mortality, ICU admission, ventilatory necessity, duration of hospital stays, adverse events.
[15]	52 vs 51	RCT open-label	Hospitalized patients	1.5 mg followed by 2 x 0.5 mg for the next 7 days, then 1 x 0.5 mg until 28 days of total treatment.	SOC	Clinical scale, Mortality, ICU admission, Mechanical ventilation
[17]	5610 vs 5730	RCT open-label	Hospitalized patients	1 mg followed by 2 x 0.5 mg per day until discharge or 10 days.	SOC	Mortality, duration of hospital stays, ventilatory support
[18]	36 vs 36	RCT double-blind	Hospitalized patients	3 x 0.5 mg (5 days) followed by 2 x 0.5 mg (5 days)	Placebo	Mortality, ICU admission, ventilatory necessity, duration of hospital stays, adverse events.
[19]	2075 vs 2084	RCT double-blind	Non-hospitalized patients	2 x 0.5 mg (first 3 days) followed by 1 x 0.5 mg 0·5 mg (27 days)	Placebo	Mortality, ICU admission, ventilatory necessity, adverse events.

RCT: Randomized controlled trial; mg: milligram; SOC: Standard of care; ICU: Intensive care unit

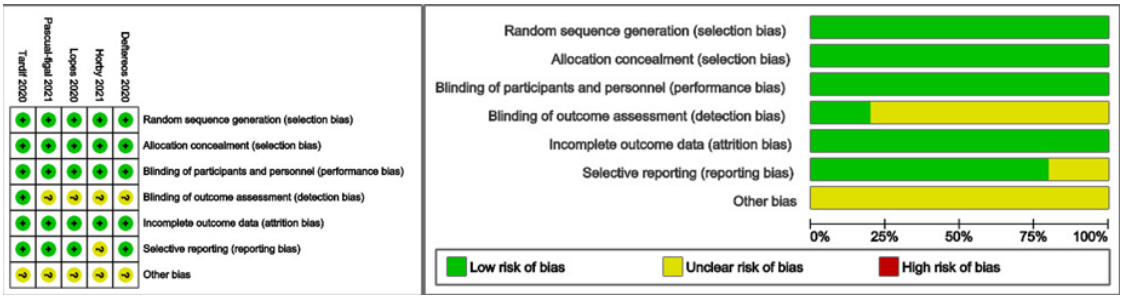

Figure 2. Assessment the risk of bias in RCTs using Cochrane collaboration tools

Colchicine has been used to treat autoimmune and inflammatory disorders [9], [10]. Recent studies suggest that colchicine has antiviral activity by inhibiting virus replication via blocking microtubule's polymerization [20], [21]. Colchicine has been found to reduce the replication of flaviviruses such as dengue and Zika [22]–[24], Colchicine also reduces respiratory syncytial virus (RSV) invasion in neonatal rats by inhibiting RSV replication, resulting in a considerable decrease in IL-6 and TNF levels [24]. Colchicine has a variety of inhibitory mechanism on macrophages, inhibit the NACHT-LRRPYD-containing protein 3 (NALP3) inflammasome and the pore formation mediated by purinergic receptors P2X7 and P2X2, along with stimulation of dendritic cell maturation and antigen presentation [25]. The activation of NACHT-LRRPYD-containing protein 3 (NLRP3) inflammasome has been shown to be activated directly by the viroporin-E of SARS-CoV-2 [12], [26], [27].

All of the included study designs were randomized controlled trials. As a control group, we included both placebo and standard care. Furthermore, the RECOVERY trial by Horby *et al*. revealed that colchicine was not associated with lower mortality rate, length of hospital stays, or risk of invasive mechanical ventilation necessity in COVID-19 patients [3]. Tardif *et al*. demonstrated a significant benefit in decreasing the risk of hospitalization and clinical worsening for COVID-19 individuals with reverse-transcriptase polymerase chain reaction (RT-PCR) confirmation who received colchicine. The mortality rate was insignificant due to the lower fatality rate [19].

3.2. Mortality rate

Five studies reported on mortality rate. As shown in Figure 3, there was no statistical difference in mortality between COVID-19 patients who were treated with colchicine and standard care (OR 1.00[95% CI 0.91-1.09], p=0.94). Chi-squared test showed fewer heterogeneity (I^2=24%).

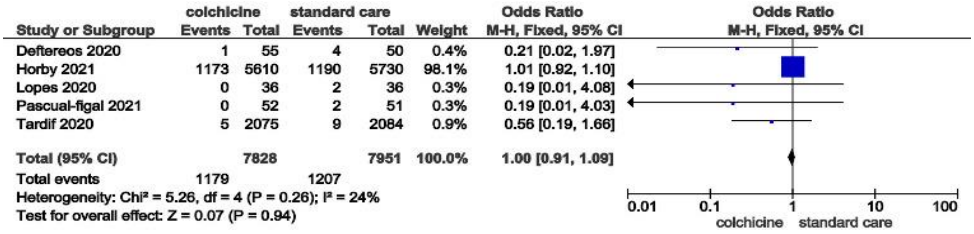

Figure 3. Forest plot of colchicine uses and mortality rate in COVID-19 patients

Colchicine was not significantly associated with a lower risk of mortality in our study, it suggests that colchicine's anti-inflammatory abilities are either inadequate to reduced mortality risk significantly or have no effect the relevant inflammatory pathways in moderate to severe COVID-19. Quite recently, the col-COVID study published the results with an open-label design in COVID-19 hospitalized patients. This study of 103 patients found that oral colchicine therapy during a 48-hour hospitalization did not significantly enhance the clinical aspect or inflammatory markers of COVID-19 patients [15]. Cure *et al*. demonstrated that since colchicine does not sufficiently decrease intracellular pH, a high viral load results in more severe cytokine storms. Additionally, toxic doses of colchicine impact alveolar type II pneumocytes, impairing surfactant release and resulting in ARDS. As a result, colchicine medication may enhance the risk of ARDS in COVID-19 pneumonia [28].

3.3. Invasive mechanical ventilation necessity

Invasive mechanical comparation ventilation necessity was observed in five studies. As shown in Figure 4, there was no statistical difference in mechanical ventilation necessity between COVID-19 patients who were treated with colchicine and those who were not (OR 0.99 [95% CI 0.83-1.17] p=0.88). Chi-squared analysis revealed moderate heterogeneity (I^2=59%).

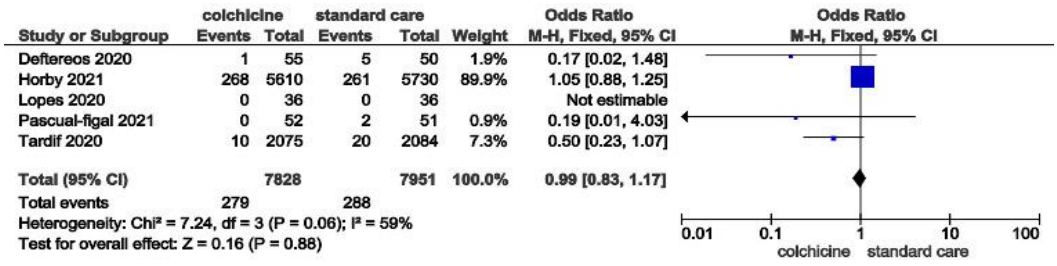

Figure 4. Forest plot of colchicine and invasive mechanical ventilation necessity in COVID-19

Pool analysis showed that colchicine was not significantly associated with lower mechanical ventilation necessity. A meta-analysis study from Siemieniuk *et al.* showed that colchicine may lower the need for mechanical ventilation in non-severe COVID-19 patients [29]. Their meta-analysis included both observational studies and RCTs, whereas we only included RCTs in our meta-analysis. Our study also included recent the large-scale randomised evaluation of COVID-19 therapy (RECOVERY) trial data, which concluded that colchicine does not affect mortality or mechanical ventilation [17].

3.4. Cardiovascular event

Cardiovascular event was compared in four studies. As shown in Figure 5, there was no statistical difference result in cardiovascular event between both interventions (OR 1.11 [95% CI 0.50-2.46], p =0.79). There was no difference regarding heterogeneity (I^2 =0%).

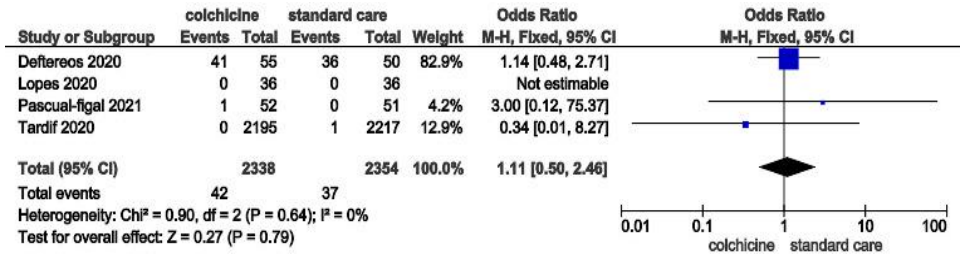

Figure 5. Forest plot of colchicine uses and cardiovascular event in COVID-19

Previous research showed that inflammation has a role in the development and progression of cardiovascular disease [30], along with anti-inflammatory therapies may reduce the risk of cardiovascular events [31]–[37]. Colchicine 0.5 mg once daily lowering the relative risk for cardiovascular mortality risk, spontaneous myocardial infarction, ischemic stroke, or ischemia-induced coronary revascularization by 31% in chronic coronary disease patients, who were previously taking proven secondary preventive therapies [38]. Our study showed that colchicine had no statistical difference in cardiovascular event between both interventions. Study about the impact of colchicine on cardiac injury in COVID-19 patients is currently still ongoing (ClinicalTrials.gov identifier: NCT04510038) [39]. COLHEART-19 study also currently in patient recruitment phase (ClinicalTrials.gov identifier: NCT04355143) [40]. The GRECCO-19 randomized controlled trial found that there were no significant changes in high-sensitivity troponin levels between colchicine groups and standard care [16]. Furthermore, colchicine had no significant effect on myocardial damage or inflammatory biomarkers during percutaneous coronary intervention [41], [42].

3.5. Gastrointestinal symptoms

Gastrointestinal symptoms as a colchicine adverse event were observed in four studies. As shown in Figure 6, patients who were treated with colchicine manifested a higher risk for gastrointestinal symptoms (OR 2.09 [95% CI 1.84-2.37], p<0.00001). Chi-squared test revealed moderate heterogeneity (I^2=45%).

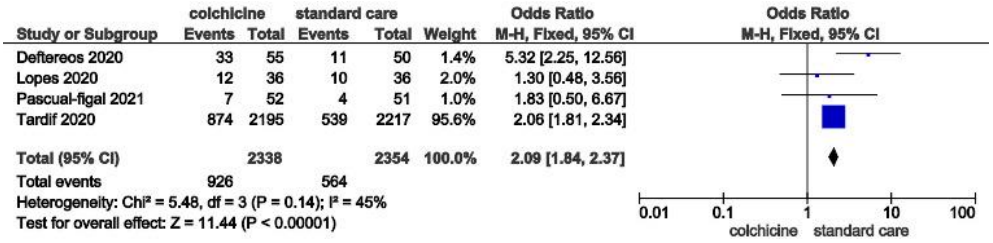

Figure 6. Forest plot of colchicine use and gastrointestinal symptom in COVID-19 patients

Colchicine is an established medication with a long history of usage among physicians [43]. The most common colchicine oral use adverse events include diarrhea (17.9% colchicine users vs. 13,1% comparator group) and gastrointestinal events (17.6% colchicine users vs. 13,1% comparator group) [44]. The side effects can be managed by lowering the dose or stopping the treatment [44]–[46]. Our study found that patients who were treated with colchicine manifested a higher risk for gastrointestinal symptoms. Specific mechanism of action by which colchicine causes diarrhea and other gastrointestinal symptoms is uncertain [47]. However, it has been suggested that it is associated with an increase in intestinal secretion, gastrointestinal motility, and prostaglandin production. In clinical studies, serious colchicine adverse effects such as liver and blood problems, neuromuscular toxicity, and death are uncommon [2], [44], [48].

3.6. Pneumonia event

In two studies, the investigators evaluated pneumonia events in COVID-19 patients in both groups. As shown in Figure 7, there is a noticeable significant difference (OR 0.68 [95% CI 0.49-0.93], p=0.02). Chi-squared analysis showed satisfying heterogeneity (I^2=0%).

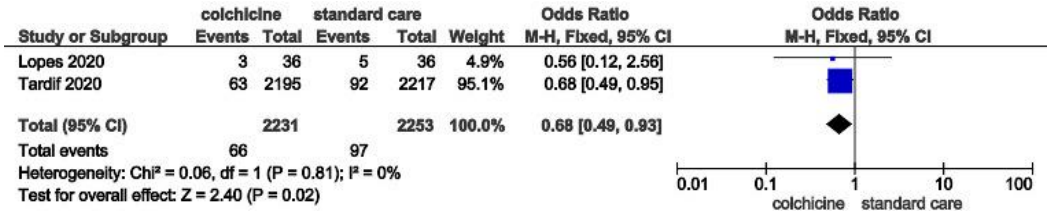

Figure 7. Forest plot of colchicine use and pneumonia

Colchicine appears to reduce the risk of viral inflammatory pneumonitis in patients with COVID-19. In an experimental animal model of acute respiratory injury, colchicine effectively decreased lung edema and notably enhanced gas exchanges, resulting in improved blood oxygenation and decreased respiratory acidosis [49]–[51]. Colchicine reduced acute lung injury by reducing lung neutrophil recruitment and reducing activation of circulating leukocytes. It is demonstrated by a 61% reduction in the injured area, a decrease in the lung injury score in damaged zone, and a decrease in alveolar wall thickness, which correlates with enhanced gas exchange [49]. Moreover, the COLCORONA study also revealed that no indication of an elevated risk of bacterial pneumonia in individuals with COVID-19 [19]. Our study has limitations, including a range in patient severity, a variable period of follow-up, and a range of colchicine doses and durations administered in each research. All of these factors could have affected the analysis conclusion.

4. CONCLUSION

Colchicine as adjuvant treatment in COVID-19 patients was not associated with lower mortality rate, invasive mechanical ventilation necessity, and cardiovascular events. Furthermore, colchicine is associated with gastrointestinal symptoms as its adverse effect. As a result, our meta-analysis concluded that routine colchicine as adjuvant treatment in COVID-19 patients was not advised.

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